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LETTER TO THE EDITOR

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Extent of inflammation in severe nasal polyposis and effect of sinus surgery on inflammation

To the editor:

Chronic rhinosinusitis with nasal polyps (CRSwNP) is, in the Western world, mainly characterized by an eosinophilic type 2 inflammation with elevated levels of immunoglobulin E (IgE), eosinophil cationic protein (ECP) and interleukin (IL)-5.[1] A subgroup of CRSwNP patients often with comorbid asthma and aspirin-exacerbated respiratory disease responds poorly to treatment and relapse after surgery.[1] A more extensive type of surgery in CRSwNP has previously been described to be successful to prevent nasal polyp relapse,[2,3] also including the frontal sinuses into the procedure. Our group recently showed that the reboot technique, with the focus on the removal of the sinus mucosa down to the periosteum in all affected sinuses, with or without a Draf III procedure, reduced relapse rates compared to conventional mucosa-sparing surgery compared to conventional mucosa-sparing surgery.[4] The aim of this study was to investigate the extent of inflammation in the sinuses associated with nasal polyposis and to understand the impact of reboot surgery on local and systemic inflammatory markers. For information on the reboot technique and postoperative treatment, see the methodological section in the Appendix S1.

During reboot surgery, tissue samples, both polyps and non-polypoid sinus mucosa, from the different sinuses, polyps in the nose and a biopsy from the middle turbinate were collected (in total 76 samples, for numbers of samples from each location please see Table S2). Inferior turbinate biopsies from healthy patients were used as controls. Twenty-one patients undergoing reboot surgery were followed up for 1 year, and nasal secretions and serum samples were collected prior to surgery and after 1 year. Nasal secretions and serum from healthy patients participating in the GA^{2}LEN cohort[5] were used as controls. Tissue, nasal secretions and serum were analysed for type 2 inflammatory markers.

The study demonstrated that IgE, ECP and IL-5 were elevated in all sinuses compared to controls, and IgE and ECP were also elevated in the middle turbinate of CRSwNP patients compared to controls. The inflammation was equally present in polyps and in non-polypoid mucosa (Figure 1 and Tables S2 and S3). There was no significant difference between single sinuses for any of the cytokines; moreover, paired analysis between polypoid and non-polypoid tissue within the same sinus of individual patients did not show any significant difference.

CRSwNP patients at inclusion had elevated levels of type 2 inflammatory markers compared to controls. Reboot surgery reduced levels of IgE, ECP and IL-5 in nasal secretions, a reduction that persisted 12 months after surgery; however, type 2 markers in nasal secretions did not reach levels of controls (Table 1). MPO and IL-17 did not show a significant reduction.

No change was seen in type 2 markers in serum (Table S4). For pre-and postoperative symptom scores and clinical outcome, please see the results part in Appendix S1 and Figure S1.

Our results show that the inflammation in CRSwNP is not limited to the polyps themselves but is equally present in the non-polypoid sinus mucosa. This non-polypoid mucosa is not addressed during conventional sinus surgery and might maintain extensive inflammation and inflammatory triggers leading to relapse. Moreover, the inflammation is widespread and includes all the different sinuses. Computed tomography studies after treatment with biologicals have previously shown a reduction of opacification in all sinuses (total Lund-Mackay scores) in severe CRSwNP patients[6,7] supporting our notion of widespread disease. These findings support the rationale of a complete surgery, the reboot approach, to prevent relapse of disease in severe CRSwNP patients. Type 2 inflammatory markers in nasal secretions were reduced after reboot surgery, at least for 12 months after surgery, but did not reach the same levels as in healthy controls. This reduction of type 2 markers resembles findings from CRSwNP treated subjects with a novel monoclonal antibody, dupilumab.[8] Our group has previously shown that the inferior turbinates in CRSwNP patients contain elevated levels of type 2 inflammatory markers.[9] Here, we show that the middle turbinates also express elevated levels of IgE and ECP, however, without forming nasal polyps. The persistent inflammation in the middle and inferior turbinates may explain why inflammatory levels in nasal secretions do not decrease to the same levels as in healthy controls after surgery. Extensive sinus surgery is debated, and removing all mucosa down to the periosteum raises concerns of causing severe complications and scar formation postoperatively. However, in our patients, healthy mucosa covered the sinus walls within a period of 4-6 weeks postoperatively, and this mucosa showed all elements of normal structured ciliated epithelium with activated goblet cells.[4] This is a small study of a novel surgical approach, and our findings need to be confirmed in a larger setting.

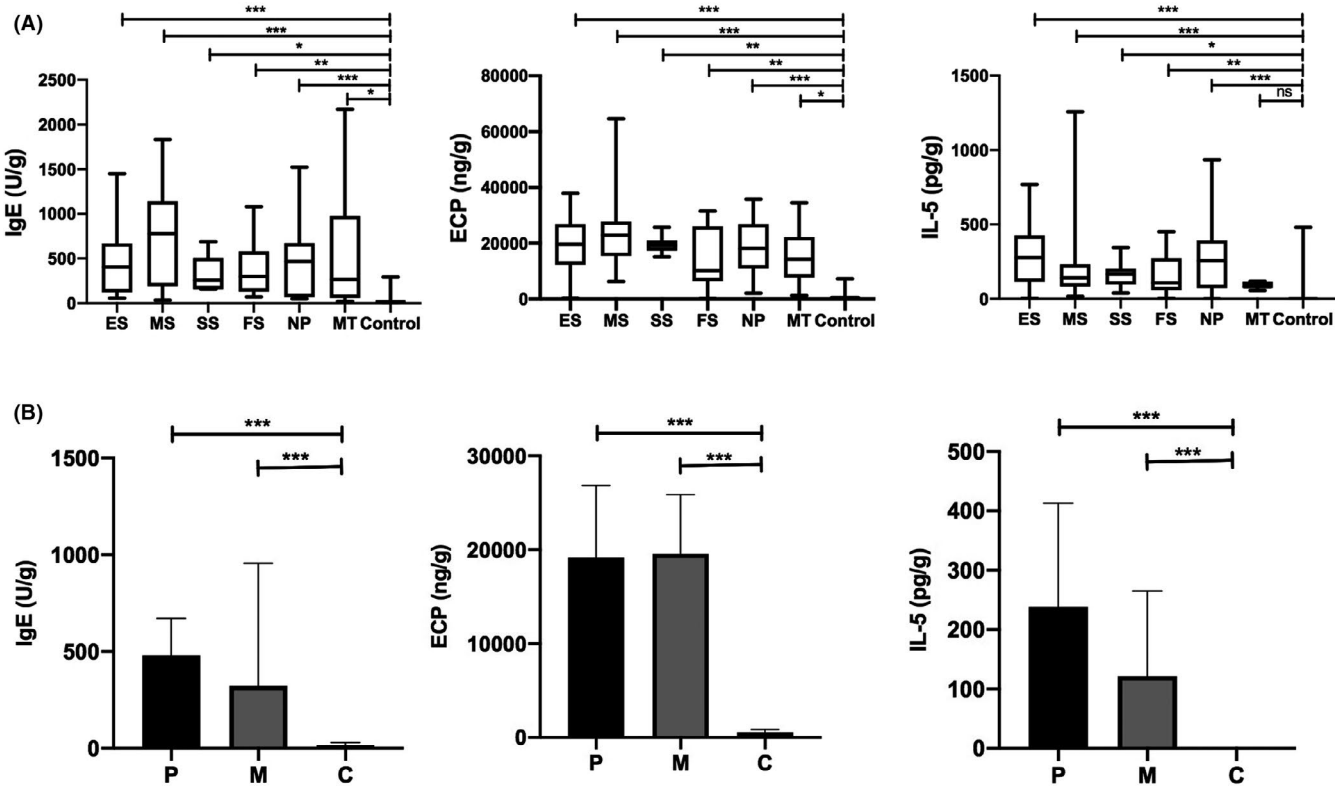

FIGURE 1 A, Levels of IgE, ECP and IL-5 in sinus mucosa, both polyps and non-polypoid sinus mucosa, from the different sinuses, nasal polyp, middle turbinate and controls. The boxes indicate the median and IQR and whiskers min; max; Kruskal-Wallis test with Dunn's multiple comparison. B, Levels of IgE, ECP and IL-5 in polyps (P), non-polypoid sinus mucosa (M) and controls (C). The boxes indicate the median and whiskers IQR; Kruskal-Wallis test with Dunn's multiple comparison. ***$P \leq .001$, **$P \leq .01$, *$P < .05$, ns; not significant. ECP, eosinophil cationic protein; ES, ethmoid sinus; MS, maxillary sinus; SS, sphenoid sinus; FS, frontal sinus; NP, nasal polyp; MT, middle turbinate

TABLE 1 Levels of type 2 markers in nasal secretions in CRSwNP at inclusion and at 12 mo' follow-up and in controls

Nasal secretions	Inclusion	12 mo	Controls	*P*-value[a]	*P*-value[a]	*P*-value[b]
N	21	21	13	I vs C	12 mo vs C	I vs 12 mo
IgE kU/L median (IQR)	53.3 (8.8;185.8)	20.6 (4.9;96.11)	2.8 (1.7;4.7)	.0002*	.006*	.03*
ECP µg/L median (IQR)	1030 (182.3;1650)	482.1 (126;1288)	42.4 (24.2;243.7)	.002*	.04*	.04*
IL-5 pg/mL median (IQR)	33.7 (2.4;309.2)	5.1 (2.1;62.6)	Not detectable	—	—	.04*
MPO pg/mL median (IQR)	9.7×10^6 (1.936×10^6;29.362×10^6)	10.127×10^6 (3.9×10^6;19.6×10^6)	2826 (244.2;6333)	<.0001	<.0001	.6
IL-17 pg/mL median (IQR)	11.3 (3.3;22.7)	9.8 (4.1;20.6)	27.8 (14.4;40.58)	.14	.15	.7

Note: P-value obtained by Kruskal-Wallis test with Dunn's multiple comparison ([a]) and Wilcoxon matched pair signed rank test ([b]). Significant *P*-values are indicated with (*).

Abbreviations: 12 mo, 12 months; C, control; ECP, eosinophil cationic protein; I, inclusion.

In conclusion, the inflammation in CRSwNP is extensive and involves polyps and non-polypoid mucosa. Reboot surgery decreases inflammatory markers 12 months after surgery. We propose that our results should be taken into consideration when planning the extent of surgery in severe CRSwNP patients. The reboot technique should however be reserved for massive, difficult to control type 2 CRSwNP patients and be performed by an experienced surgeon to avoid complications.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest. Dr Bachert reports grants from FWO Flanders, from Interuniversity Attraction Poles Grant, Ghent University, grants from the European Commission's Seventh Framework Program, and grants from Sanofi Belgium, during the conduct of the study; personal fees from Sanofi, personal fees from Novartis, personal fees from Astra-Zeneca, and personal fees from GSK, outside the submitted work; and is a member of advisory boards of Novartis, Sanofi, Astra-Zeneca and GSK.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.